Original Article

The association between statin and COVID-19 adverse outcomes: national COVID-19 cohort in South Korea

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Background: There currently exist limited and conflicting clinical data on the use of statins in coronavirus disease 2019 (COVID-19) patients. The aim of this paper was to compare hospitalized patients with COVID-19 who did and did not receive statins.

Methods: We performed a population-based retrospective cohort study using South Korea's nationwide healthcare claim database. We identified consecutive patients hospitalized with COVID-19 and aged 40 years or older. Statin users were individuals with inpatient and outpatient prescription records of statins in the 240 days before cohort entry to capture patients who are chronic statin users and, therefore, receive statin prescriptions as infrequently as every 8 months. Our primary endpoint was a composite of all-cause death, intensive care unit (ICU) admission, mechanical ventilation use and cardiovascular outcomes [myocardial infarction (MI), transient cerebral ischemic attacks (TIA) or stroke]. We compared the risk of outcomes between statin users and non-users using logistic regression models after inverse probability of treatment weighting (IPTW) adjustment.

Results: Of 234,427 subjects in the database, 4,349 patients were hospitalized with COVID-19 and aged 40+ years. In total, 1,115 patients were statin users (mean age =65.9 years; 60% female), and 3,234 were non-users (mean age =58.3 years; 64% female). Pre-hospitalization statin use was not significantly associated with increased risk of the primary endpoint [IPTW odds ratio (OR) 0.82; 95% confidence interval (CI): 0.60–1.11]. Subgroup analysis showed a protective role of antecedent statin use for individuals with hypertension (IPTW OR 0.40; 95% CI: 0.23–0.69, P for interaction: 0.0087).

Conclusions: Pre-hospitalization statin use is not detrimental and may be beneficial amongst hypertensive COVID-19 patients. Further investigation into statin is needed for more conclusive effects of statins for treatment of COVID-19.

Keywords: Statin; coronavirus disease 2019 (COVID-19); Korean National Insurance Claims data; comparative effectiveness

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Introduction

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic (1,2). Over a year later, there has now been more than 250 million cases, and more than 5 million deaths worldwide (3).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the COVID-19 disease, and its pathophysiology involves an overproduction of an early response proinflammatory cytokines, specifically tumor necrosis factor (TNF), interleukin (IL)-6 and IL-1β (4). If unabated, this cytokine storm subsequently places COVID-19 patients at increased risk of vascular hyperpermeability, multiorgan failure, and death (5).

As a result, statins have been suggested for use as a therapy for COVID-19. It is reported that statin agents can stabilize MYD88 at normal levels and reduce an ensuing cytokine storm (6). Statins may also up-regulate angiotensin-converting enzyme 2 (ACE2), which is typically downregulated by SARS-CoV-2, and thus potentially facilitate the infiltration of SARS-CoV-2 (7).

There currently exist limited and conflicting clinical data on the use of statins amongst COVID-19 patients. While many studies (8-15) reported that statin medications reduced the risk of disease severity and/or mortality, several other studies (16-20) reported no significant difference between statin users and non-users. As well, one study (21) reported an increased mortality among statin users. Meanwhile, a recent systematic review and meta-analysis of 110,078 patients reported a reduced risk of mortality among those administered statins after their COVID-19 hospitalization, but no difference in patients who were administered statins before hospitalization (22). Although there is a lack of consensus among data on efficacy and safety of statins amongst COVID-19 patients, the current recommendation is for COVID-19 patients to continue any antecedent statin use (23).

Given the limited and conflicting data, there is a need for further and more rigorous investigation into the relationship between statin use and COVID-19 outcomes. The aim of this analysis was to compare hospitalized patients with COVID-19 who did and did not receive statins before hospitalization, in terms of COVID-19 outcomes. Our hypothesis was that antecedent statin use is associated with decreased incidence of all-cause death, intensive care unit (ICU) admission, mechanical ventilation use and cardiovascular outcomes [myocardial infarction (MI), transient cerebral ischemic attacks (TIA) or ischemic stroke]. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3464/rc).

Methods

Data source and study population

We used the database from project #OpenData4Covid19, an international collaborative research project hosted by the Ministry of Health and Welfare (MoHW) of South Korea and the Health Insurance Review and Assessment Service (HIRA). The HIRA is a nationwide governmental agency providing a review of health insurance claims and a fee-for-service reimbursement (24), covering 98% of the Korean population (approximately 50 million people). The database consists of history of claims for 234,427 consecutive individuals for SARS-CoV-2 infection from January 1st to May 15th, 2020 in South Korea. Specifically, information gathered in the dataset includes sociodemographic characteristics, healthcare utilization history, diagnosis results [International Classification of Diseases, 10th Revision (25); ICD-10] and prescription from both inpatient and outpatient settings.

Between January 1st and May 15th, 2020, 7,590 individuals tested positive for COVID-19. A positive COVID-19 result was defined as a positive result from a diagnostic test that used a reverse-transcription polymerase chain reaction method approved by the South Korean Ministry of Food and Drug Safety per WHO recommendation (26). Individuals were excluded if they were younger than 40 years old, since younger patients are less likely to experience severe adverse outcomes after COVID-19 infection regardless of statin use and therefore inclusion of younger patients may undermine the effects of statins. As well, statin use is less common in these younger patients and its use might be associated with higher risk features that are less generalizable to the general public. We also excluded individuals who were not hospitalized for precise outcome assessment. As a result, 4,349 individuals were included in the sample cohort (*Figure 1*). Cohort entry was defined as the date of admission for COVID-19 hospitalization. Most of these patients were hospitalized until fully recovery. A full recovery was defined as cessation of fever without medication use, and two consecutive negative test results within a 24-hour period (27).

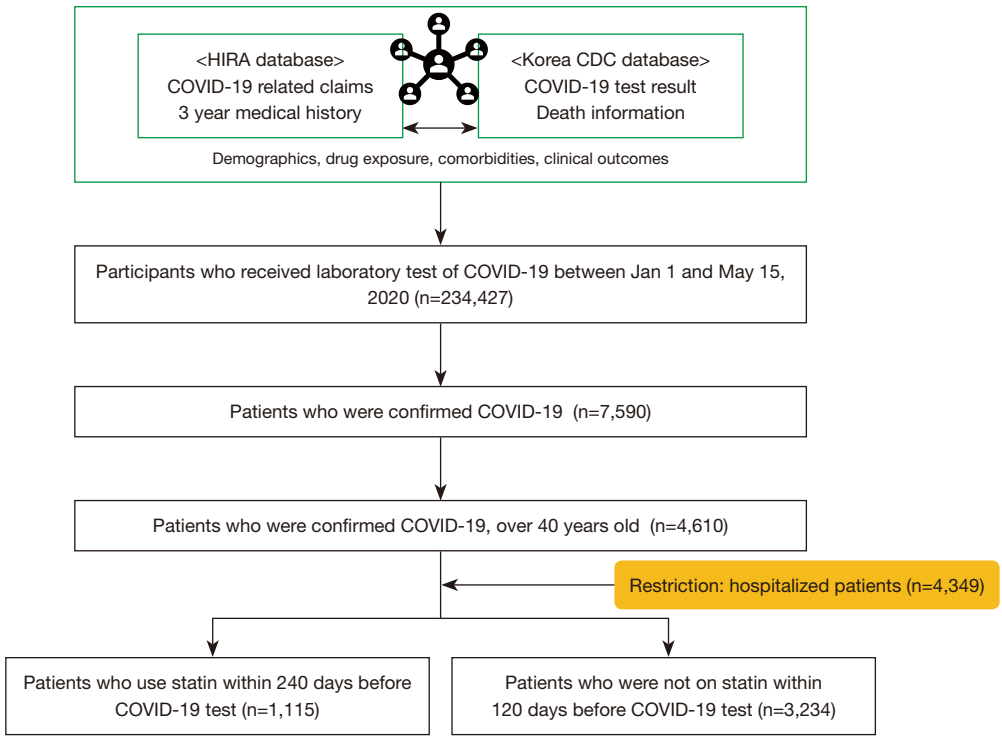

Figure 1 Population-based cohort study design using the HIRA and KDCA database of South Korea. HIRA, Health Insurance Review and Assessment Service; COVID-19, coronavirus disease 2019; CDC, Centers for Disease Control and Prevention; KDCA, Korean Disease Control and Prevention Agency.

This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the South Korean MoHW, which waived the requirement of informed consent due to retrospective study design and anonymity of the HIRA database (IRB # P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Endpoints

We set the primary endpoint as a composite of all-cause death, ICU admission, mechanical ventilation use and cardiovascular outcomes (MI, TIA or ischemic stroke). As secondary endpoints, we measured the components of the composite endpoint individually. All endpoints were defined using in-hospital ICD-10 diagnostic codes and the national procedure coding system (Table S1). We measured study endpoints between the date of cohort entry and the earliest of the date of hospital discharge or end of study period (May 15, 2020), whichever occurred earlier.

Exposures

We defined exposure by using inpatient and outpatient prescription records of statin medications from the HIRA database. Patients prescribed statins within 240 days prior to cohort entry were regarded as statin users, and otherwise patients were defined as non-users. The prescription of statin was defined by Anatomical Therapeutic Chemical (ATC) codes (Table S1). Our definition follows an intention-to-treat approach.

Statistical analysis

For descriptive statistics, we presented mean and standard deviation for continuous variables and frequency and percentage for categorical variables. We compared baseline characteristics for statin users and non-users with absolute standardized difference (aSD). aSD $\leq$0.1 was preferred for indicating balance while aSD $\leq$0.2 was deemed acceptable.

For outcome analysis, we estimated odds ratio (OR) from a logistic regression analysis incorporated with the

inverse probability of treatment weighting (IPTW). First, we estimated the propensity score (PS) of prescribing statin from a logistic regression, where the predictors include age in years, square of age, sex, and health insurance type at cohort entry, 20 pre-exposure comorbidities and 12 pre-exposure co-medications (Appendix 1). We defined comorbidity variables from in-hospital ICD-10 diagnostic codes and co-medications from in/out-hospital ATC codes (Table S1). We assigned the inverse probability of treatment (IPT) weight to each individual in the cohort, 1/PS to the statin users, and 1/(1–PS) to the non-users, to construct a balanced pseudo-population. Then, weighted univariable logistic regressions were fitted to estimate the effect of statin use on primary and secondary endpoints. We reported the estimated OR and its 95% confidence interval (CI). For comparison, we also considered unweighted logistic regression: both univariable and multivariable, adjusted for age, sex, insurance type, history of diabetes mellitus and history of hypertension.

To study the association effect per subgroups, we conducted outcome analysis stratified the cohort by (I) age (<65 and ≥65 years) and (II) sex for the risk of the primary endpoint. We also considered stratification by the history of (III) hyperlipidemia, (IV) hypertension, and (V) diabetes mellitus. To examine the effect modification, P value for interaction from each stratification was assessed (P for interaction).

We performed several sensitivity analyses. We re-estimated the OR with modified data where all confirmed positive individuals of at least 40 years of age were included into the study population regardless of their hospitalization record. The time window for ascertaining exposure extended from 240 to 360 days to include statin users who get statin prescription annually. In addition, we considered alternative choices of statistical methods: (I) conducting the main IPTW analysis with discarding individuals with extreme PS values (IPTW with trimming); (II) including the estimated PSs as an additional predictor to other covariates (outcome adjustment model); (III) the stabilized mortality ratio weighting (SMRW) instead of IPTW; and (IV) PS matching instead of IPTW.

Results

A total of 4,349 adults of at least 40 years of age were hospitalized with COVID-19 in South Korea between January 1, 2020 and May 15, 2020 and included this analysis. Of these, 1,115 (26%) were statin users. Statin users were older than non-users on average (65.9±11.2 *vs.* 58.3±12.3 years). Among statin users, 39.6% were males, whereas 36.1% of non-users were male. A larger proportion of statin users had comorbidities of coronary artery disease (16.8% *vs.* 3.6%), chronic lung disease (50.6% *vs.* 24.6%), diabetes mellitus (40.3% *vs.* 10.7%), hyperlipidemia (65.4% *vs.* 18.1%), and hypertension (53.5% *vs.* 17.7%), relative to non-users. Statin users also used more antidiabetic (35.6% *vs.* 6.4%) and antiplatelet (37.7% *vs.* 7.9%) medications (*Table 1*). All variables after the adjustment achieved aSD ≤0.1 except for anxiolytics (aSD =0.12).

Among 530 primary composite events of all-cause death, ICU admission, mechanical ventilation use and cardiovascular adverse outcomes, 362 occurred in non-users (11.2%; 362/3,234) and 168 (15.1%; 168/1,115) in statin users. No significant difference was noted between statin users and non-users in the IPTW weighted analysis (IPTW adjusted OR 0.82; 95% CI: 0.60–1.11). Similarly, there was no difference between statin users and non-users for the individual components of all-cause death, mechanical ventilation, ICU admission, and cardiovascular adverse outcome (*Table 2*).

In the subgroup analyses, there existed a significant effect modification by hypertension status (P for interaction =0.0087). Statin users who had hypertension experienced lower odds for the composite (IPTW OR 0.40, 95% CI: 0.23–0.69). There was no effect modification by age, sex, hyperlipidemia and diabetes mellitus (*Table 3*).

The results from the sensitivity analyses remained generally consistent with the main analysis with no harmful effects of statin use on the endpoints. When redefining the study population, changing the exposure ascertainment window and applying other statistical methods, the primary endpoint, all-cause death, ICU admission and cardiovascular outcomes, showed generally similar results. For example, statins showed protective effects on the primary endpoint (SMRW adjusted OR 0.64, 95% CI: 0.45–0.93; PS matching OR 0.74, 95% CI: 0.56–0.98). The protective effects of statins persisted for primary endpoint, when including all confirmed patients with COVID-19 (SMRW adjusted OR 0.58, 95% CI: 0.40–0.88; PS matching OR 0.76, 95% CI: 0.57–0.99). For all-cause deaths, statins showed protective effects (SMRW adjusted OR 0.56, 95% CI: 0.35–0.89; PS matching OR 0.67, 95% CI: 0.45–0.98). The protective effects of statins persisted for all-cause deaths, when including all confirmed patients with COVID-19 (SMRW adjusted OR 0.49, 95% CI: 0.29–0.84). For ICU admission, statin showed protective effects when

Table 1 Baseline sociodemographic and clinical characteristics of study patients with statin users and non-users

Characteristic	Before IPTW			After IPTW[§]		
	User[#] (N=1,115) (25.6%)	Non-user (N=3,234) (74.4%)	aSD	User (N=4,099)	Non-user (N=4,505)	aSD
Age (years), mean ± SD	65.9±11.2	58.3±12.3	0.64	61.1±13.2	60.9±12.9	0.01
40–49	79 (7.1)	829 (25.6)		892 (21.8)	893 (19.8)	
50–59	252 (22.6)	1,155 (35.7)		1,080 (26.3)	1,432 (31.8)	
60–69	379 (34.0)	684 (21.2)		1,097 (26.8)	1,066 (23.7)	
70–79	259 (23.2)	312 (9.6)		549 (13.4)	644 (14.3)	
80–89	131 (11.7)	202 (6.2)		415 (10.1)	380 (8.4)	
90+	15 (1.3)	52 (1.6)		67 (1.6)	90 (2.0)	
Sex						
Male	442 (39.6)	1,167 (36.1)	0.07	1,703 (41.5)	1,673 (37.1)	0.09
Female	673 (60.4)	2,067 (63.9)	0.07	2,397 (58.5)	2,832 (62.9)	0.09
Health insurance type						
Medical insurance	960 (86.1)	2,871 (88.8)	0.08	3,490 (85.1)	3,952 (87.7)	0.08
Medical aid	155 (13.9)	363 (11.2)	0.08	610 (14.9)	553 (12.3)	0.08
Comorbidities						
Arrhythmia	46 (4.1)	62 (1.9)	0.13	112 (2.7)	116 (2.6)	0.01
Asthma	144 (12.9)	279 (8.6)	0.14	400 (9.8)	458 (10.2)	0.01
Atrial fibrillation	36 (3.2)	35 (1.1)	0.15	63 (1.5)	72 (1.6)	0.00
Autoimmune disease	117 (10.5)	272 (8.4)	0.07	303 (7.4)	396 (8.8)	0.05
Chronic lung disease	564 (50.6)	794 (24.6)	0.56	1,425 (34.8)	1,487 (33.0)	0.04
Coronary artery disease	187 (16.8)	118 (3.6)	0.44	320 (7.8)	349 (7.7)	0.00
Dementia	98 (8.8)	189 (5.8)	0.11	371 (9.1)	330 (7.3)	0.06
Diabetes mellitus	449 (40.3)	345 (10.7)	0.72	910 (22.2)	933 (20.7)	0.04
Heart failure	87 (7.8)	90 (2.8)	0.23	200 (4.9)	213 (4.7)	0.01
Hyperlipidemia	729 (65.4)	585 (18.1)	1.09	1,335 (32.6)	1,480 (32.9)	0.01
Hypertension	596 (53.5)	571 (17.7)	0.81	1,197 (29.2)	1,332 (29.6)	0.01
Ischemic stroke or TIA	156 (14.0)	129 (4.0)	0.36	324 (7.9)	350 (7.8)	0.00
Kidney disease	28 (2.5)	28 (0.9)	0.13	65 (1.6)	71 (1.6)	0.00
Liver disease	44 (3.9)	146 (4.5)	0.03	295 (7.2)	214 (4.8)	0.10
Malignancy	61 (5.5)	146 (4.5)	0.04	223 (5.4)	248 (5.5)	0.00
Other cerebrovascular diseases	112 (10.0)	125 (3.9)	0.24	252 (6.1)	279 (6.2)	0.00
Peripheral vascular disease	144 (12.9)	207 (6.4)	0.22	398 (9.7)	368 (8.2)	0.05
Pneumonia including tuberculosis	95 (8.5)	204 (6.3)	0.08	411 (10.0)	339 (7.5)	0.09

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Before IPTW			After IPTW[§]		
	User[#] (N=1,115) (25.6%)	Non-user (N=3,234) (74.4%)	aSD	User (N=4,099)	Non-user (N=4,505)	aSD
Psychiatric disorders	357 (32.0)	690 (21.3)	0.24	1,197 (29.2)	1,132 (25.1)	0.09
Thromboembolism	120 (10.8)	93 (2.9)	0.32	246 (6.0)	248 (5.5)	0.02
Co-medications						
Acetaminophen	610 (54.7)	1,475 (45.6)	0.18	1,970 (48.1)	2,210 (49.1)	0.02
Antibiotics systemic	840 (75.3)	2,167 (67.0)	0.18	2,778 (67.8)	3,114 (69.1)	0.03
Anticoagulants	93 (8.3)	76 (2.4)	0.27	173 (4.2)	207 (4.6)	0.02
Antidementia	146 (13.1)	263 (8.1)	0.16	490 (12.0)	457 (10.2)	0.06
Antidepressants	199 (17.8)	361 (11.2)	0.19	667 (16.3)	620 (13.8)	0.07
Antidiabetics	397 (35.6)	207 (6.4)	0.77	647 (15.8)	727 (16.1)	0.01
Antiplatelets	420 (37.7)	254 (7.9)	0.76	722 (17.6)	842 (18.7)	0.03
Antipsychotics	269 (24.1)	682 (21.1)	0.07	1,100 (26.8)	1,037 (23.0)	0.09
Antivirals	79 (7.1)	223 (6.9)	0.01	284 (6.9)	298 (6.6)	0.01
Anxiolytics	390 (35.0)	777 (24.0)	0.24	1,329 (32.4)	1,213 (26.9)	0.12
Immunosuppressant	630 (56.5)	1,524 (47.1)	0.19	2,061 (50.3)	2,255 (50.1)	0.00
NSAIDs	917 (82.2)	2,437 (75.4)	0.17	3,091 (75.4)	3,468 (77.0)	0.04

Mean and standard deviation were reported for continuous variables. Frequency and percentage were reported for categorical variables. [§], weighted cohort using the IPTW; [#], patients prescribed within 240 days prior to cohort entry were regarded as statin users, and otherwise patients were defined as non-users. IPTW, inverse probability of treatment weighting; aSD, absolute standardized difference; TIA, transient cerebral ischemic attack; NSAIDs, nonsteroidal anti-inflammatory drugs.

redefining exposure window to 360 days (IPTW-trimming adjusted OR 0.67, 95% CI: 0.47–0.97) (Tables S2,S3).

Discussion

This study reported on one of the largest investigations of COVID-19 patients with hospitalization in South Korea. It utilized a nationwide and completely enumerated dataset and applied a PS-based weighting to control for potential confounding variables. In the main analysis, there was no significant difference between baseline (pre-hospitalization) statin users and non-users with respect to the composite endpoint of mortality, ICU admission, mechanical ventilation use and cardiovascular outcomes.

Although results of our main analysis showed statistically insignificant association between statin and primary endpoint, it is possible that we missed detecting a real protective association of statin in the main analysis, especially since some of sensitivity analysis showed protective association of statin for primary endpoint, all cause death and ICU admission based on varying statistical methods such as SMR weighting and PS matching, changing the exposure window change to 360 days, and inclusion of non-hospitalized COVID-19 patients. These results are in contrast to the findings from the two recently published randomized controlled trials (28,29). In the Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia: A Pragmatic Randomized Controlled Trial (29), the combined use of rosuvastatin 40 mg once daily with colchicine and emtricitabine/tenofovir reduced the risk of 28-day mortality and the need for invasive mechanical ventilation in hospitalized patients with pulmonary compromise from COVID-19. In the Intermediate *vs.* Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomised

Table 2 Association between COVID-19 adverse clinical outcomes and statin use

Outcomes	Cumulative incidence, n (%)		Unadjusted*		Adjusted[§]		IPTW adjusted[#]	
	Non-user	User	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Composite primary endpoint	362 (11.2)	168 (15.1)	1.41 (1.16–1.71)	<0.0001	0.87 (0.70–1.09)	0.24	0.82 (0.60–1.11)	0.20
All-cause death	131 (4.1)	86 (7.7)	1.98 (1.50–2.62)	<0.0001	0.97 (0.70–1.34)	0.83	0.90 (0.58–1.39)	0.62
Mechanical ventilation use	66 (2.0)	57 (5.1)	2.59 (1.80–3.71)	<0.0001	1.41 (0.94–2.09)	0.09	1.24 (0.74–2.09)	0.08
ICU admission	233 (7.2)	97 (8.7)	1.23 (0.96–1.57)	0.11	0.97 (0.73–1.28)	0.82	0.72 (0.49–1.05)	0.08
Cardiovascular adverse outcomes[♭]	31 (1.0)	15 (1.3)	1.41 (0.76–2.62)	0.28	1.17 (0.60–2.29)	0.64	0.79 (0.32–1.97)	0.62

*, unweighted univariable logistic regression model; [§], unweighted multivariable logistic regression model adjusted for age, sex, insurance type, history of diabetes mellitus and history of hypertension; [#], IPTW-weighted univariable logistic model; [♭], cardiovascular adverse disease included myocardial infarction, ischemic stroke and TIA. COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; TIA, transient cerebral ischemic attack.

Table 3 OR and 95% CI of composite primary in subgroups

Group	N	Cumulative incidence, n (%)		IPTW adjusted OR	
		Non-user	User	OR (95% CI)	P value
Total	4,349	362 (11.2)	168 (15.1)	0.82 (0.60–1.11)	0.20
Age (years)					P for interaction* =0.17
<65	2,944	168 (7.0)	47 (8.7)	1.06 (0.65–1.73)	0.82
≥65	1,405	194 (23.4)	121 (21.0)	0.67 (0.43–1.03)	0.07
Sex					P for interaction =0.79
Male	1,609	168 (14.4)	88 (19.9)	0.72 (0.43–1.21)	0.22
Female	2,740	194 (9.4)	80 (11.9)	0.79 (0.51–1.23)	0.29
Hyperlipidemia					P for interaction =0.44
No	3,035	292 (11.0)	60 (15.5)	0.90 (0.60–1.35)	0.61
Yes	1,314	70 (12.0)	108 (14.8)	0.71 (0.45–1.11)	0.13
Hypertension					P for interaction =0.0087
No	3,182	259 (9.7)	69 (13.3)	1.00 (0.67–1.51)	0.98
Yes	1,167	103 (18.0)	99 (16.6)	0.40 (0.23–0.69)	0.001
Diabetes mellitus					P for interaction =0.34
No	3,555	293 (10.1)	91 (13.7)	0.86 (0.59–1.26)	0.43
Yes	794	69 (20.0)	77 (17.1)	0.60 (0.32–1.12)	0.11

*, P value for the interaction term for each stratification. OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

Controlled Trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) (28) of patients admitted to ICU, a subgroup of patients who presented within 7 days of symptom onset showed lower odds of the primary efficacy outcome (venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause

mortality) when they had received atorvastatin 20 mg once daily, compared with patients who got placebo. Both studies report a potentially beneficial effect of antecedent statin use, and suggests that statin use may have a protective effect in the early inflammatory phase.

In our prespecified subgroup analysis, statin use showed lower odds of the primary endpoint in hypertensive patients. As hypertensive COVID-19 patients are known to have poorer prognosis than normotensive patients (30), this result is encouraging; statins may have greater protective effects among patients with hypertension. Daniels *et al.* (31) reported similar findings of a protective association for severe COVID-19 outcomes among statin users, in patients with hypertension and/or cardiovascular disease. These pronounced protective association of statin among hypertensive patients could be from statin's effect on treating underlying cardiovascular disease, as Daniels *et al*. Proposed. However, Lohia *et al*. (12) reported no protective association between statin and severe COVID-19 outcome among hypertensive patients, but did report a protective association among patients with diabetes mellitus. No similar finding was found in our cohort, but this may be due to our cohort's much lower event rate (7.7% mortality rate among statin user), which could have decreased the power to detect the effect of statin in our cohort's subgroups. Furthermore, our cohort's ethnic composition may play a role here—the majority of individuals in our cohort were Korean, compared to the majority being Black in Lohia *et al.*'s study (12). Of final note, our cohort had a much lower event rate that other hospitalization cohorts, as most of the COVID-19 patients in Korea were hospitalized according to a national policy to contain infection, regardless of patient's symptoms. Among all confirmed COVID-19 patients ≥40 years of age (n=4,610), 94.3% were hospitalized (n=4,349) regardless of symptom presence in our population.

Further investigation is needed since statins may be cost-effective with the potential benefit outweighing any potential toxicities (32). Mechanistically, statins are postulated to upregulate ACE2, countering the effect of SARS-CoV-2, where ACE2 is downregulated and thereby facilitates the infiltration of SARS-CoV-2 (7). Although statins can cause rare muscle and liver side effects, discontinuation of statins treatment is a known way to reverse these side effects, alleviating concerns of significant and irreversible adverse effects. As of January 19, 2022, 12 randomized clinical trials to assess the effect of statins in COVID-19 patients were registered on the clinicaltrials.gov website (NCT02735707, NCT04952350, NCT04904536, NCT04900155, NCT04801940, NCT04631536, NCT04472611, NCT04466241, NCT04380402, NCT04348695, NCT04333407, NCT02344290) which may help elucidating true effect of statin among COVID-19 patients.

This study has several strengths. First, we used a nationwide cohort of all hospitalized patients with COVID-19 in South Korea between January 1st and May 15th, 2020. Since South Korea maintained a strict patient management system during this period with mandatory admission requirement for the majority the confirmed COVID-19 patient, the use of this population-based cohort mitigated any potential sampling bias issue. In addition, our study design further mitigated healthy user bias by including chronic co-medications as confounders, which may have adjusted for past adherence (33). Furthermore, our main findings of no harmful effects of statin on COVID-19 outcomes were reaffirmed by our sensitivity analyses. In fact, they showed protective effects when we redefined the study population, extended the ascertainment period of the statin use, and considered various statistical approaches. Given these neutral to protective effects of statin on COVID-19 outcomes, our findings endorse the current guideline to continue statin in COVID-19 patients who have previously been treated with statins (23).

There are also several limitations of this study. First, there may have been outcome misclassification in cardiovascular outcomes (MI, stroke, and TIA), because we defined our cardiovascular outcome variables by diagnostic codes in admirative claim data. The HIRA reported that 82% of primary diagnosis codes in claims coincide with electronic medical records (34), so more than 18% of outcome misclassification can occur while trying to capture all the diagnostic codes other than primary diagnosis codes. However, we expect a greater validity for MI, stroke, and TIA since our study population focused on hospitalized patients under careful management. Other outcomes such as all-cause death seem to be well classified because the HIRA COVID-19 database was linked to the national death records and outcomes defined from procedure codes (ICU admission and mechanical ventilation use) are also expected to be valid since the codes are mandatory in the reimbursement review process. Second, statin exposure was defined based on inpatient and outpatient prescriptions. We were not aware of detailed information on the exposure, for example, adherence to the prescription. Lastly, although we performed IPTW and thorough sensitivity analyses,

there might still be a residual confounding by potential unmeasured confounders typically used in clinical studies (e.g., body weight, body mass index, baseline blood pressures, laboratory test values) due to the inherent limitation of claims data.

In conclusion, our analysis of a nationwide sample of South Korean, hospitalized COVID-19 patients found that statin users overall did not experience poorer COVID-19 outcomes relative to non-users. However, in hypertensive patients, protective effects of statin use on COVID-19 outcomes were shown, which warrants further investigation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the South Korean Ministry of Health and Welfare, which waived the requirement of informed consent due to retrospective study design and anonymity of the HIRA database (IRB # P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Appendix 1

Potential confounders used in estimating propensity score

We included sociodemographic and clinical factors that are considered to be associated with both statin use and risk of the outcomes. For sociodemographic factors, we included age in years, square of age, sex, and health insurance type at cohort entry. We included clinical variables of 20 pre-exposure comorbidities (arrhythmia, asthma, atrial fibrillation, autoimmune disease, chronic lung disease, coronary artery disease, dementia, diabetes mellitus, heart failure, hyperlipidemia, hypertension, kidney disease, liver disease, malignancy, other cerebrovascular diseases, peripheral vascular disease, pneumonia including tuberculosis, psychiatric disorders, stroke or TIA, thromboembolism) and 12 pre-exposure co-medications (acetaminophen, antibacterials, anticoagulants, antidementia, antidepressants, antidiabetics, antiplatelets, antipsychotics, antivirals, anxiolytics, immunosuppressants, NSAIDs). The ascertainment period to define comorbidities was from 3 years prior (–1,080 d) through the start of the exposure ascertainment (–240 d). The ascertainment period to define co-medications was from 2 years prior (–720 d) through –240 d. We defined comorbidity variables from in-hospital ICD-10 diagnostic codes and co-medications from in/out-hospital anatomical therapeutic chemical codes (*Table S1*). When defining malignancy, we additionally used the expanded benefit codes in addition to diagnosis codes to reduce false-positives.

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Table S1 Definition of covariates and adverse clinical outcomes

Diagnoses	Codes
Inclusion criteria	
COVID-19 (KCD-7)	B342, B972, Z208, Z290, U18, U181, Z038, Z115, U071, U072
Confirmed (database-specific code)	'Y'
Study endpoints	
All-cause death (database-specific code)	'Y'
Intensive care unit admission (NPC)	AH110, AH190-192, AH194, AH195, AH210, AH29-299, AH390-AH396, AH398, AH399, AH501, AJ001, AJ003-011, AJ020, AJ021, AJ031, AJ043-046, AJ100, AJ102, AJ110, AJ112, AJ120, AJ122, AJ130, AJ132, AJ140, AJ142, AJ143, AJ150, AJ152 AJ160, AJ180, AJ190, AJ200, AJ202, AJ210, AJ212, AJ220, AJ222, AJ230, AJ240, AJ242, AJ250, AJ252, AJ260, AJ280, AJ290, AJ300, AJ302, AJ310, AJ312, AJ320, AJ322, AJ330, AJ332, AJ340, AJ342, AJ350, AJ352, AJ360, AJ380, AJ390, AJ500, AJ510, AJ520, AJ530, AJ540, AJ550, AJ560, AJ580, AJ590
Mechanical ventilation use (NPC)	M0850, M0857, M0858, M0860, M5830, M5850~5858, M5860, MM360, MM400
Cardiovascular adverse outcome	
Myocardial infarction	I21
Ischemic stroke	I63, I64, G463-468
TIA	G45
Comorbidities (ICD-10)	
Arrhythmia	I44, I45, I47
	(or anti-arrhythmias drug uses ATC code 'C01B')
Asthma	J45, J46
Atrial fibrillation	I48
Autoimmune disease	
Rheumatoid arthritis	M05, M06
Systemic connective tissue disorder	M30-M36
Noninfectious enteritis and colitis, ulcerative colitis, Crohn's disease	K50-K52, R652, R653
Idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia	D693, D59
Psoriatic arthritis, juvenile rheumatoid arthritis, Ankylosing spondylitis	M07, M08, M45
Other interstitial pulmonary disease	J84
Transplanted status, rejection	Z97, T86
Glomerular disease	N00-N08
Lupus	L93, M32
Intestinal malabsorption, celiac disease	K90
Multiple sclerosis, myasthenia gravis	G35, G700
Vasculitis	M05
Autoimmune thyroiditis, polyglandular failure, hepatitis	E063, E31, K754
Psoriasis	L40, L41, M07, M09
Sarcoidosis	D86, G532, M633
	(or immunosuppressants drug uses ATC codes 'L04A', 'H02', 'P01BA')
Chronic lung disease	
Bronchiectasis	J47
Chronic obstructive pulmonary disease	J40, J41, J43, J44, E11
Interstitial pulmonary disease	J84
Coronary artery disease	
Coronary artery disease	I20-I25
Atherosclerosis	I70
Dementia	F00, F01, F02, F03, G30, G3100, G3182
Diabetes mellitus	E10-E14
Heart failure	
Heart failure	I110, I50
Valvular heart disease	I34, I35, I36, I37
Hyperlipidemia	E78
Hypertension	I10-I15
	(or Anti-hypertensive drug uses ATC codes 'C09A', 'C09B', 'C09C', 'C09D', 'C07', 'C08', 'C03', 'C01D', 'C02A', 'C02B', 'C02C')
Ischemic stroke or TIA	
Ischemic stroke	I60-I64, G463, G464, G465, G466, G467, G468
TIA	G45
Kidney disease	
Acute kidney failure	N17
Chronic kidney disease (CKD)	N18, N19
Liver disease	
Chronic liver disease	K70-K77
Viral hepatitis	B15-B19
Malignancy	C00-C97
	(and expanded benefit coverage codes 'V027', 'V193', 'V194')
Other cerebrovascular diseases	G46, I65, I66, I67, I68, I69
Peripheral vascular disease	I70-I79
Pneumonia including tuberculosis	
Tuberculosis	A15, A16, A17, A18, A19
Pneumonia	J12, J13, J14, J15, J16, J17, J18
Psychiatric disorders	F04-F99
Thromboembolism	I26, I63, I74, I801, I802, I803, I809, I82
Study drugs (ATC)	
Statin	
Atorvastatin	C10AA05, C10BA05, C10BA08, C10BX03, C10BX06, C10BX08, C10BX11, C10BX12, C10BX15
Cerivastatin	C10AA06
Fluvastatin	C10AA04
Lipid lowering agents	C10AA, C10AA01-08, C10BA, C10BA01-09, C10BX, C10BX01-17, A10BH51, A10BH52
Lovastatin	C10AA02, C10BA01
Pitavastatin	C10AA08
Pravastatin	C10AA03, C10BA03, C10BX02
Rosuvastatin	C10AA07, C10BA06, C10BA07, C10BA09, C10BX05, C10BX07, C10BX09, C10BX10, C10BX13, C10BX14, C10BX16, C10BX17, A10BH52
Simvastatin	C10AA01, C10BA02, C10BA04, C10BX01, C10BX04, A10BH51
Co-medications (ATC)	
Acetaminophen	N02BE01, N02BE05, N02BE51, N02BE71
Antibacterials	J01
Anticoagulants	B01AA, B01AB, B01AE, B01AF, B01AX
Antidementia	N06D
Antidepressants	N06A
Antidiabetics	A10
Antiplatelets	A01AD05, C07FX02, C07FX03, C07FX04, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, M01BA03, N02AJ02, N02AJ07, N02AJ18, N02BA01, N02BA51, N02BA71, B01AC
Antipsychotics	N05A
Antivirals	J05
Anxiolytics	N05B
Immunosuppressants	L04A (L04AA, L04AB, L04AC, L04AD, L04AX), H02, P01BA
NSAIDs	M01A

ATC, Anatomical Therapeutic Chemical classification code; COVID-19, coronavirus disease 2019; KCD-7, Korean Standard Classification of Diseases 7th Revision; ICD-10, International Classification of Disease 10th Revision; NPC, national procedure codes; TIA, transient cerebral ischemic attack; NSAIDS, nonsteroidal anti-inflammatory drugs.

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Table S2 Sensitivity analysis redefining the study population and the exposure ascertainment window

Characteristic	Cumulative incidence, n (%)		IPTW adjusted OR	
	Non–user	User	OR (95% CI)	P value
Redefining study population (all confirmed patients)				
Composite primary endpoint	368 (10.7)	174 (14.7)	0.77 (0.56–1.05)	0.09
All–cause death	135 (3.9)	91 (7.7)	0.81 (0.51–1.28)	0.37
Mechanical ventilation use	66 (1.9)	57 (4.8)	1.18 (0.73–2.06)	0.43
ICU admission	235 (6.8)	99 (8.4)	0.70 (0.48–1.02)	0.07
Cardiovascular adverse disease	31 (0.9)	15 (1.3)	0.80 (0.33–1.96)	0.62
Redefining time window for ascertaining exposure (~360 d)				
Composite primary endpoint	335 (11.2)	175 (15.0)	0.77 (0.57–1.03)	0.08
All-cause death	126 (4.0)	91 (7.8)	0.87 (0.57–1.33)	0.51
Mechanical ventilation use	65 (2.0)	58 (5.0)	1.17 (0.71–1.94)	0.53
ICU admission	230 (7.2)	100 (8.6)	0.67 (0.47–0.97)	0.03
Cardiovascular adverse disease	31 (1.0)	15 (1.3)	0.84 (0.36–1.97)	0.69

IPT, inverse probability of treatment; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

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Table S3 Sensitivity analysis applying alternative statistical methods

Characteristic	IPTW adjusted with trimming		Outcome adjusted		SMRW adjusted		PS matched	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Main analysis								
Composite primary endpoint	0.77 (0.57–1.03)	0.20	0.82 (0.64–1.06)	0.14	0.64 (0.45–0.93)	0.02	0.74 (0.56–0.98)	0.04
All-cause death	0.87 (0.57–1.33)	0.62	0.84 (0.59–1.21)	0.35	0.56 (0.35–0.89)	0.02	0.67 (0.45–0.98)	0.04
Mechanical ventilation use	1.18 (0.71–1.95)	0.41	1.18 (0.77–1.95)	0.40	1.09 (0.63–1.90)	0.76	1.03 (0.63–1.70)	0.90
ICU admission	0.67 (0.47–0.97)	0.08	0.79 (058–1.09)	0.15	0.67 (0.42–1.06)	0.09	0.77 (0.54–1.10)	0.15
Cardiovascular adverse disease	0.84 (0.36–1.98)	0.62	1.13 (0.36–1.98)	0.77	0.61 (0.16–2.26)	0.46	0.93 (0.36–2.39)	0.88
Redefining study population (All confirmed patients)								
Composite primary endpoint	0.76 (0.56–1.05)	0.10	0.81 (0.65–1.05)	0.12	0.58 (0.40–0.88)	0.01	0.76 (0.57–0.99)	0.05
All-cause death	0.81 (0.51–1.29)	0.37	0.84 (0.59–1.20)	0.34	0.49 (0.29–0.84)	0.01	0.69 (0.48–1.00)	0..05
Mechanical ventilation use	1.21 (0.76–1.92)	0.43	1.23 (0.73–2.06)	0.43	1.11 (0.64–1.92)	0.71	1.03 (0.62–1.69)	0.92
ICU admission	0.70 (0.48–1.02)	0.07	0.79 (0.58–1.08)	0.14	0.70 (0.44–1.11)	0.13	0.78 (0.55–1.11)	0.17
Cardiovascular adverse disease	0.80 (0.33–1.96)	0.62	1.11 (0,50–2.46)	0.80	0.64 (0.18–2.29)	0.49	0.93 (0.36–2.38)	0.88
Redefining time window for ascertaining exposure (~360 d)								
Composite primary endpoint	0.77 (0.57–1.03)	0.08	0.80 (0.62–1.02)	0.08	0.71 (0.48–1.04)	0.08	0.77 (0.59–1.01)	0.06
All-cause death	0.87 (0.56–1.33)	0.51	0.87 (0.61–1.25)	0.46	0.66 (0.40–1.10)	0.11	0.77 (0.53–1.13)	0.18
Mechanical ventilation use	1.17 (0.71–1.94)	0.53	1.12 (0.70–1.77)	0.64	1.13 (0.65–1.99)	0.67	1.02 (0.62–1.67)	0.94
ICU admission	0.67 (0.47–0.97)	0.03	0.75 (0.55–1.02)	0.07	0.73 (0.45–1.17)	0.19	0.76 (0.54–1.07)	0.11
Cardiovascular adverse disease	0.84 (0.36–1.97)	0.69	1.02 (0.47–2.25)	0.95	0.72 (0.22–2.35)	0.58	0.86 (0.34–2.18)	0.76

IPTW, inverse probability of treatment weighting; SMRW, stabilized mortality ratio weighting; PS, propensity score; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

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